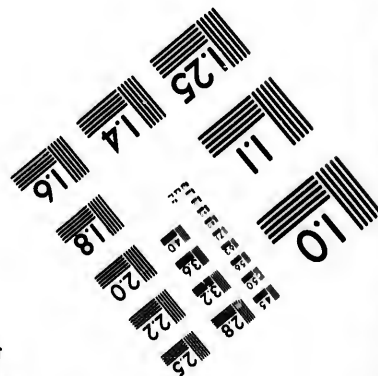
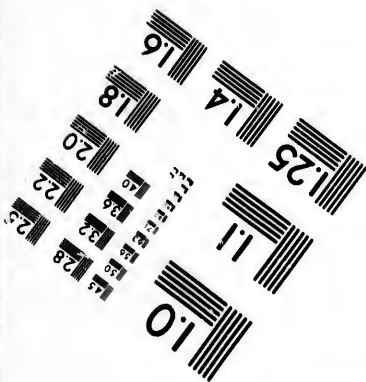
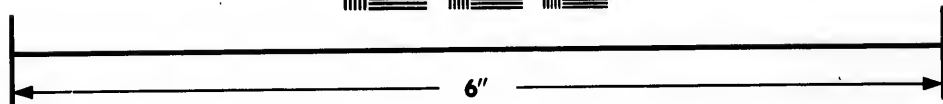
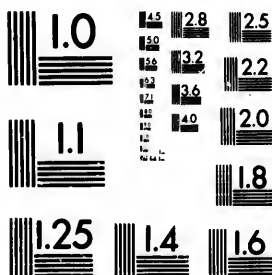


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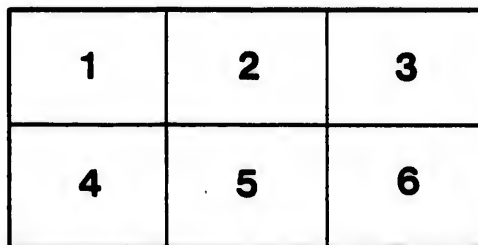
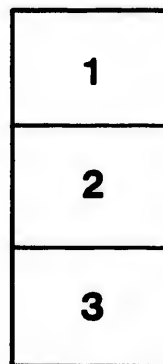
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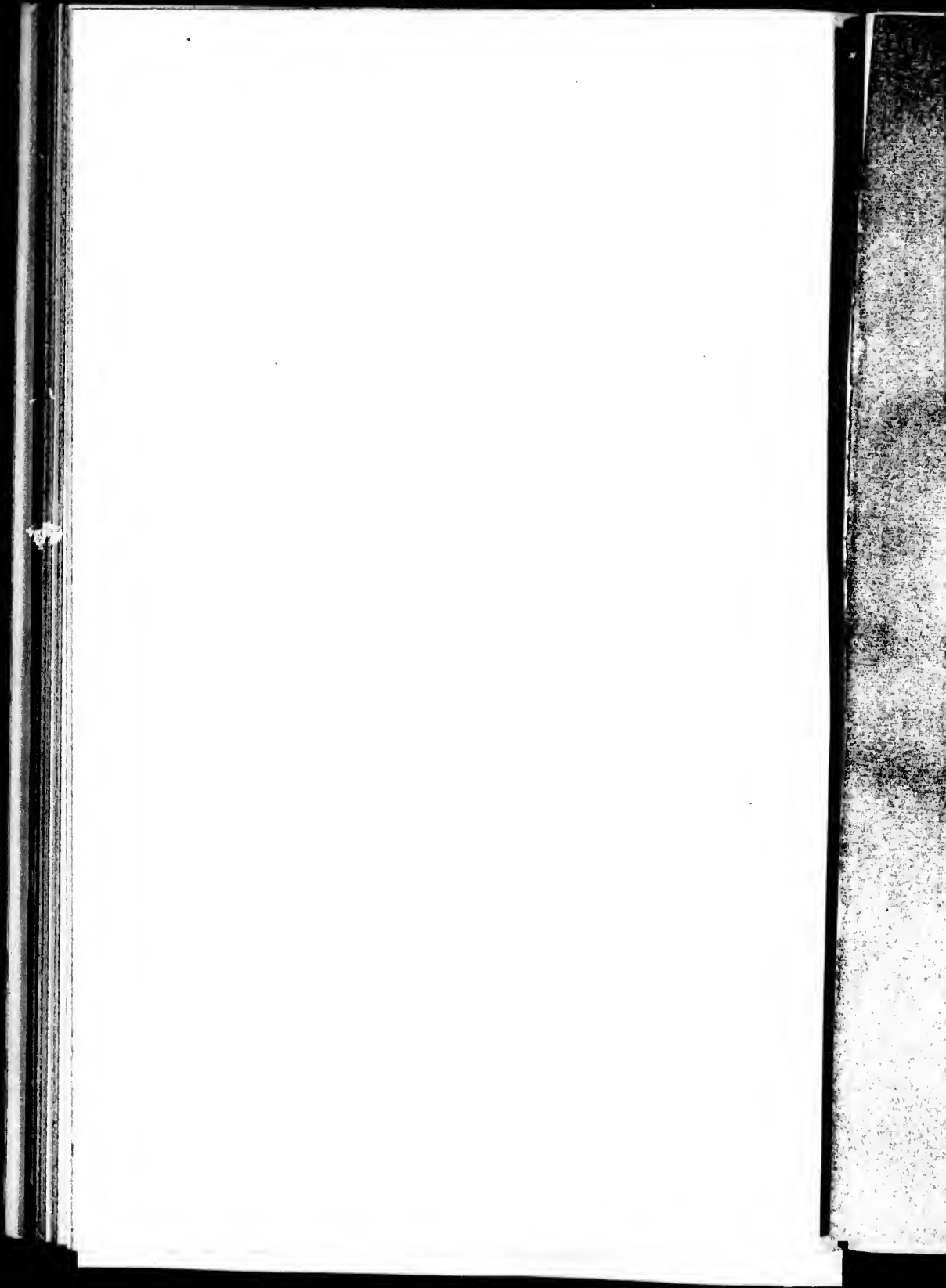
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ON THE DIAGNOSTIC VALUE OF  
TUBERCULIN

C. F. MARTIN, B.A., M.D.

Lecturer on Medicine, McGill University; Assistant Physician,  
Royal Victoria Hospital, Montreal.

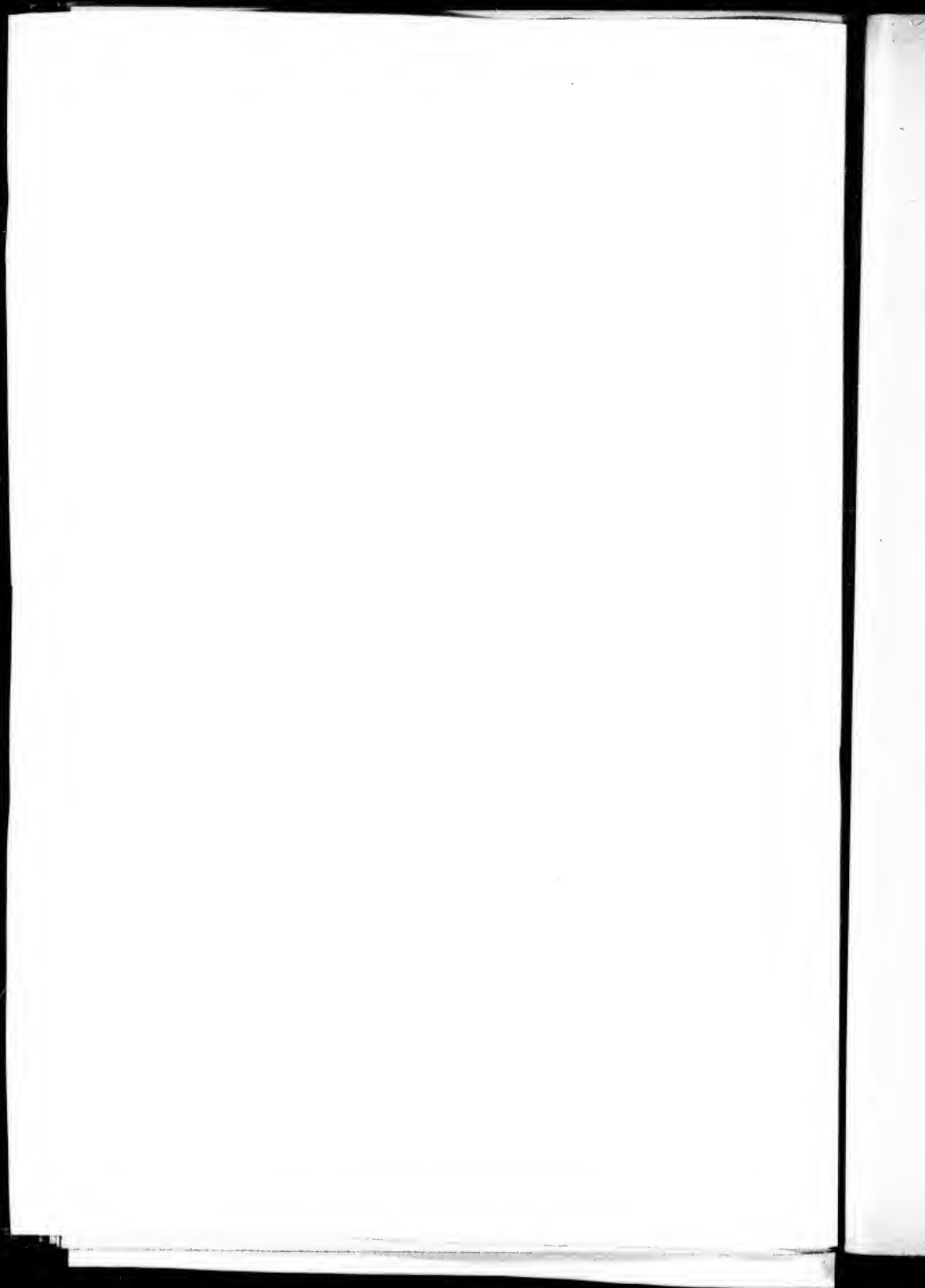
AND

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*(From the Medical Clinic of the Royal Victoria Hospital, Montreal)*

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## ON THE DIAGNOSTIC VALUE OF TUBERCULIN.

BY

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AND

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It is now more than six years since tuberculin was placed before the medical world as a possible reagent for the diagnosis of tuberculosis. Its employment in veterinary science is now so universal and so productive of accurate results that not to use it is to stigmatise oneself as being of low rank in that profession. For human tuberculosis, too, it was at first employed with considerable success, though within a short time its value seemed indeed dubious, and as a diagnostic agent it fell more or less into disrepute. This, however, resulted mainly from two hypotheses, neither of which could be completely substantiated when the perfected method of using tuberculin had been employed. It was feared in the first place that the injections would rekindle quiescent foci in the tissues, or transform a local phthisis to a disseminated condition. Instances are on record where this seems undoubtedly to have occurred, but the doses were evidently far in excess of those now employed. Certainly it cannot be said that any recent observers, in injecting 5 mg. or less of tuberculin, have ever had evil results attributable directly or indirectly to the injection.

Another and more appreciable reason for the disfavour into which the tuberculin test has grown is the apparently contradictory



results which have followed its employment. Cases of undoubted tuberculosis have failed to react, while, *per contra*, patients in whom there was no demonstrable evidence of the disease have often afforded pronounced reactions. We have ourselves met not infrequently with instances of tuberculosis where a reaction failed, and are inclined to believe that the fault lies mainly in one of three conditions: Firstly, early cases of pure tuberculosis may fail to react through insufficient dosage; secondly, we have commonly observed that where marked mixed infection is present, the reactions may be much less pronounced, or at times quite absent; and, thirdly, patients suffering from advanced phthisis are often quite incapable of reaction from the very nature of their impoverished tissues and their impaired metabolism. We will refer to this, however, later on.

It is certainly a curious circumstance that the test should so have fallen into disrepute in face of the most noteworthy results obtained by the German authorities, many of whom, after prolonged investigations, strongly advocated its advantages as a diagnostic aid. Senator, for example, who examined 46 cases of tuberculosis, obtained a positive reaction in every instance; 4 others among his cases, however, apparently non-tuberculous, likewise reacted to the reagent, a fact which at the time was not satisfactorily explained. This point, indeed, introduces an important feature of the literature, inasmuch as the proofs of the presence of tuberculosis cannot depend on clinical investigation alone. It is impossible to say of any individual from physical examination that there is no tuberculous lesion in his body; and hence the difficulties of proving the fallacies of the test in this regard. The experience of advanced veterinarians along these lines should certainly carry an important weight; and they bear out in every respect the value of the reagent. Time and again a positive reaction has been obtained in cattle which have been considered by sceptics in every way healthy; and examinations have been made *post mortem*, only to show the tuberculous focus somewhere or other, though often so very minute as almost to escape detection, consisting frequently of merely some bean-sized caseous gland in the mesentery or mediastinum.

It does not seem unfair to apply the same analogy to human beings, and to assert that the presence of a decided reaction must indicate that somewhere or other tuberculosis does exist, even though

the stethoscope and pleximeter fail to detect it. Certainly the proofs on the analogy of bovine tuberculosis are more than striking; and it may reasonably be hoped that some day it will be computed as great an error to say that people not having tuberculosis may react to tuberculin, as it was of the oriental observer to assert that malarial plasmodia existed in conditions other than paludism; in other words, to argue in that way is virtually begging the question. One cannot be blamed for regarding the question in this light; the very prevalence of tuberculosis argues in its favour; and the hundreds—nay, thousands—of tuberculous cases that come yearly to the necropsy table, in which no such conditions had ever been detected *intra vitam*, must surely be considered before we assert on physical grounds alone that tuberculin is reacting in people who are free from the disease.

The results of Finkler are even more striking than those of Senator, inasmuch as of 73 cases of tuberculosis 71 reacted positively and only 2 failed, while again the best results recorded by any observers are probably those of Guttman. In the latter's interesting series of 62 cases he has had but one instance which renders the test even dubious. His figures include in the first place 14 healthy people who were inoculated, and with negative results, and 8 more patients ill with general diseases other than tuberculosis, who equally gave negative results. The remaining 40 patients examined were all tuberculous, and in every instance gave positive reactions when the tuberculin was injected.

The cases above referred to presented mainly pulmonary or intestinal tuberculous lesions; but equally good results were obtained in the surgical clinics where the tests were employed for external tuberculosis, thus confirming the original statements made by Koch concerning its diagnostic value. Trendelenburg, for example, examined in this way some 90 cases, including cutaneous, arthritic, and genitourinary tuberculosis, and in only one instance did he obtain a negative result. His experience showed that for some reason a tuberculosis of the testis excited a reaction less readily than did that of any other part. The researches of Mikulicz, Doutrelepont, and others merely confirm those of Trendelenburg.

With reference to contradictory results, there are such striking instances as those of Mosler, who found a reaction in 17 out of 21 non-

tuberculous patients. One may safely say on general principles, however, that when one or two isolated observers obtain results diametrically opposed to most others who are undertaking similar experiments, something is lacking either in the methods and technique or in the conception of the work; whether Mosler's ideas of what constitutes a reaction differ from others we cannot say, failing his original paper, but it seems difficult to conceive how his investigations are correct when such a host of opposing testimony is arrayed against him.

In our own observations we have not been able as yet to trace the unlimited results in all the patients in whom tuberculosis was suspected, and where a reaction was obtained; but, nevertheless, we may safely say that the sum total of our investigations has afforded a decided and satisfactory record in favour of the great diagnostic value of tuberculin.

Following upon the suggestions of Dr. E. L. Trudeau, it has been our practice to commence with an initial injection of  $\frac{1}{2}$  to 1 mg., according as the patient was a child or an adult. Failing a reaction, we have waited two or three days, and then employed a second dosage of 2 mg.; and when no reaction followed, a final dose of 3 mg. was given two or three days later. When under such conditions a negative result supervened, we have concluded that no tuberculosis was present, though in one instance this conclusion proved absolutely false.

With reference to the advent of evil results, which have been declared by many authorities to be either inevitable or at all events possible, we can only state that in not a single instance has any trouble arisen of the nature either of a local or general injury. Where the tuberculous patients were inoculated, there was never any evidence from which to adduce suspicions of increased lesions or a more acute trouble; while, through due regard to cleanliness, the site of inoculation never occasioned any anxiety. Not infrequently there was local redness, pain, and tumefaction, but never any further sign of infection or abscess formation. So far as the alleged dangerous general symptoms are concerned, such as collapse or syncope or erythemata, we have had no experience with them whatever, the reaction itself being the only manifestation noteworthy.

In our own observations in the hospitals we have noted mainly the following features:

1. Results of injection in patients where no clinical signs of tuberculosis could be detected, and where no suspicion of such a condition was present.
2. Results in undoubted cases of tuberculosis.
3. Examination of doubtful cases, such as pleurisy with effusion, pyonephrosis, etc.
4. Surgical tuberculosis, where efforts were made to remove all the tuberculous tissue present.

To satisfy ourselves on the first of these points, cases were employed of the most varied nature, the only requirement being that no appreciable amount of fever was present. There were tested thus, for example, 7 cases of chronic rheumatism, 5 cases of organic and functional nervous diseases, 4 of organic heart disease, 5 of pulmonary diseases other than tuberculosis, and a number of other maladies referable to one or other of the organs or tissues of the body. The series included in all more than 30 cases, and in not one instance was there a rise of temperature or constitutional disturbance sufficient to warrant even a suspicion of a positive reaction to the tuberculin. The dosage was employed in most of the cases as above stated, and the results were eminently satisfactory.

Perhaps in none of these instances was there so striking an advantage in employing the test as in several cases of slowly-resolving pneumonia, where from a period of from five to six weeks after the acute symptoms had subsided, there was evidence of consolidation of the lung, and just such a condition as might be incident to a tuberculous process. The inoculations, however, proved negative, and a favorable prognosis was in each instance given to the relatives, while the course of the disease later on to recovery amply justified the conclusions drawn. In another case of pyuria the diagnosis of tuberculosis had seemed undoubted, though careful preparations of the urinary sediment had failed to reveal the bacilli of tuberculosis. Tuberculin, when injected, gave negative results, and the subsequent operation revealed merely the presence of a renal calculus, the removal of which was attended by progressive amelioration and ultimate recovery.

Of the cases of undoubted tuberculosis tested, only those were employed where there was practically an absence of fever, or fever so

slight as not to interfere with the reaction. The inoculations, too, were given at night, so that any possible rise might occur during the time of day when least of all we would anticipate a tuberculous pyrexia.

Of these, 5 were cases of undoubted pulmonary tuberculosis, 4 of tuberculous pleurisy, 1 patient with tuberculosis and pyopneumothorax, and also one with genito-urinary tuberculosis. In all, positive reactions were obtained. Cases with Pott's disease and morbus coxæ gave similar results, and, as a rule, marked reactions. Six were successfully inoculated in this manner, though 2 others failed to react. In each of these latter there was wasting, and a large local cold abscess associated with the primary disease. Two cases of tuberculous cervical adenitis were injected, and gave positive reactions, as did also 3 cases of tuberculous arthritis of the knee-joint.

With reference to the third point, namely, the observation of doubtful cases, such as pleurisy, where the etiology was obscure, there was some difficulty in accurately establishing the value of the test. The attempt was made to inoculate the pleural effusions into guinea-pigs, and thus to insure a diagnosis of tuberculosis in suspected cases; but, in common with other observers, we here obtained negative results. In all cases, likewise, the suggestions of Eichhorst to inoculate the fluid in large quantities were followed, but the results, even so, proved quite unsatisfactory.

Again, where patients failed to react, and where it was believed that no tuberculosis was present, the cases after leaving the hospitals never reappeared for examination.

Apart, however, from the 4 undoubted cases above mentioned, were 2 others in whom at first there was merely a suspicion of tuberculosis of the pleura. The diagnosis in these, established by the inoculation of the tuberculin, was later verified by development of the disease in the lungs. In one of these cases an insidious onset of the effusion and significant family history aroused the suspicion of its bacillary origin, but a guinea-pig inoculated with the fluid was unaffected; the injection, however, of  $\frac{1}{2}$  mg. of tuberculin was followed by marked rigors, *malaise*, and a temperature of  $104.4^{\circ}$ . In the course of a few weeks the pleural effusion subsided, and the patient left the hospital greatly improved; two months later she returned to the out-

door department, with definite signs of pulmonary destruction in the apex of the previously affected side, obviously a tuberculous condition. The case before mentioned where a pyuria gave difficulties in diagnosis is likewise of interest in this connection, as showing the value of the reaction in clearing up obscure cases.

The examinations of cases in which operations have been performed for the removal of tuberculous tissue has just been commenced, and we have injected but two patients, both of whom had undergone excision of the knee-joint. Both patients reacted mildly to the tuberculin; although there was no discoverable evidence of remaining lesion, local or elsewhere. Our investigations, however, are still in progress.

It will be seen from the cases just recorded that more than 30 patients in whom no tuberculosis could be discerned failed to respond in any degree to the inoculation of the reagent; that on the other hand, 21 cases of undoubted tuberculosis reacted positively. Several failures remain to be recorded, however, these having occurred under small doses of the tuberculin, and before we had become aware that a dose larger than three milligrammes was sometimes necessary. Guttman, in his long series of cases, had observed that with a dose of 3 milligrammes he invariably obtained as marked a reaction as with any larger dose; but our own observations have led us to conclude that at times there is an individual susceptibility or idiosyncrasy which enables a very small dose to produce a marked reaction, while in other instances no result is obtained till a larger quantity is administered. It is in this way we would account for a distinct failure in a young man with incipient pulmonary tuberculosis, showing very few local signs, but in whose sputum tubercle bacilli were found. The inoculation of three successive doses of 1, 2 and 3 milligrammes was attended with negative results; and believing it wiser at the time not to administer more, the patient was allowed to leave the hospital before a larger dose could be injected. In one case of tuberculous tarsitis, and one of Pott's disease, the same negative results were obtained with similar small doses; but with these instances ends the total number of cases where the diagnostic value of the test seems doubtful.

As to the criterion of what constitutes a reaction, there has evidently been considerable variation of opinion. In our own cases,

unless the rise of temperature was more than  $1\frac{1}{2}^{\circ}$  to  $2^{\circ}$  F. above that previously existing, we have not considered the reaction positive; and usually the febrile condition subsided gradually in about thirty-six to forty-eight hours. In the majority of cases the constitutional symptoms were slight, including mainly headache and slight *malaise* with nausea. Distinct rigors were uncommon. The highest temperature obtained was  $105^{\circ}$  F., and that after the injection of only  $\frac{1}{2}$  milligramme.

In conclusion, we would record our hearty thanks to Drs. Trudeau and Hewetson, of Saranac Lake, for their manifold kindly suggestions and generous supply of tuberculin, while we are further indebted to the clinicians in attendance at the General and Royal Victoria Hospitals for the use of material so freely granted.

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